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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/825,995	04/16/2004	Niels Christian Kaarsholm	6573.204-US	9239

23650 7590 01/24/2007

NOVO NORDISK, INC.
PATENT DEPARTMENT
100 COLLEGE ROAD WEST
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EXAMINER	
BRADLEY, CHRISTINA	
ART UNIT	PAPER NUMBER
1654	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	01/24/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/825,995	KAARSHOLM ET AL.	
	Examiner	Art Unit	
	Christina Marchetti Bradley	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 October 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-220* is/are pending in the application.

4a) Of the above claim(s) *2-126,171-204,219 and 220* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,127-170 and 205-218* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *7/26/2004*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election of Group XI, claims 127-170, and the species on page 5 in the reply filed on 10/26/2006 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

2. Claims 2-126, 171-204, 219 and 220 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim.

Specification

3. The disclosure is objected to because of the following informalities: the application number does not appear on the first page. Appropriate correction is required.

Claim Objections

4. Claims 127, 145-149 and 155-157are objected to because of the following informalities: the use of bullets. Commas or semicolons would be easier to interpret. Appropriate correction is required.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 127-170 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The phrases "valence bond" in claims 127-135, 152 and 153, "ArG1"

in claims 137-139, 146 and 147, "Het1" in claim 137, "Het2" in claim 138, "Het3" in claims 139 and 146 are undefined rendering the formulas indefinite.

Claim Rejections - 35 USC § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

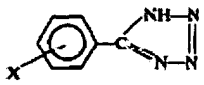
> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

9. Claims 1, 205 and 213-218 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dunn (U.S. Patent No. 5,830,999) in view of Franke & Groeneveld (*Transit. Met. Chem.*, **1981**, *6*, 54-6). Dunn teaches that ligands that bind tightly and specifically to the two His^{B10} Zn^{2+} sites in insulin stabilize formulations of insulin hexamers for pharmaceutical use (abstract). Regarding claim 205, Dunn teaches compositions of fast acting insulin (column 7, line 7). Regarding claims 213-216, Dunn teaches compositions of at least 2 moles of zinc per mole of insulin (column 7, line 19) and at least 22 moles of phenolic compound per insulin hexamer (column 6, line 60). Regarding claims 217 and 218, Dunn teaches compositions with isotonicity agents and buffers (column, 7, line 11). Dunn does not teach the specific zinc ligands of the claimed invention. Franke & Groeneveld teach that tetrazoles can coordinate zinc. It would have been obvious to one of ordinary skill in the art to combine the tetrazole ligands of Franke &

Groeneveld with the insulin hexamers of Dunn. The skilled artisan would have been motivated to do so given that Dunn teaches that ligands for the His^{B10} Zn^{2+} sites stabilize the hexamer form of insulin and Franke & Groeneveld teach that tetrazole containing compounds can coordinate zinc. There would have been a reasonable expectation of success given that the tetrazole compounds of Franke & Groeneveld are functionally equivalent to the ligands of Dunn. Thus, the invention as a whole was clearly *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

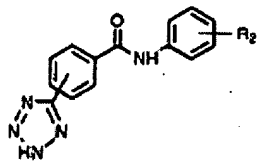
10. Claims 1, 127-140, 150-153, 155-157, 205 and 213-218 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dunn (U.S. Patent No. 5,830,999) in view of Franke & Groeneveld (*Transit. Met. Chem.*, **1981**, *6*, 54-6) and Ciarkowski *et al.* (*Org. Mag. Res.*, **1979**, *12*, 631-6). Dunn teaches that ligands that bind tightly and specifically to the two His^{B10} Zn^{2+} sites in insulin stabilize formulations of insulin hexamers for pharmaceutical use (abstract). Regarding claim 205, Dunn teaches compositions of fast acting insulin (column 7, line 7). Regarding claims 213-216, Dunn teaches compositions of at least 2 moles of zinc per mole of insulin (column 7, line 19) and at least 22 moles of phenolic compound per insulin hexamer (column 6, line 60). Regarding claims 217 and 218, Dunn teaches compositions with isotonicity agents and buffers (column, 7, line 11). Dunn does not teach the specific zinc ligands of the claimed invention. Franke & Groeneveld teach that tetrazoles can coordinate zinc. Ciarkowski *et al.* teach the following tetrazole compounds:



where X can be methyl, $-N(CH_3)_2$, $-NH_2$, $-OCH_3$, -OH, -COOH, -I, -Br, -Cl, -CN, or $-NO_2$ at the 2, 3 or 4 positions. With respect to the formula in claim 127, K is a bond, M is an arylene, R^{40} is a halogen, -CN, $-NO_2$, OR^{41}, $-NR^{41}R^{42}$, R^{41} and R^{42} are H or methyl, Q is a bond and T is hydrogen. It would have been obvious to one of ordinary skill in the art to combine the tetrazole ligands of Ciarkowski *et al.* with the insulin hexamers of Dunn. The skilled artisan would have been motivated to do so given that Dunn teaches that ligands for the His^{B10} Zn^{2+} sites stabilize the hexamer form of insulin and Franke & Groeneveld teach that tetrazole containing compounds can coordinate zinc. There would have been a reasonable expectation of success given that the tetrazole compounds of Ciarkowski *et al.* are functionally equivalent to the ligands of Dunn. Thus, the invention as a whole was clearly *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

11. Claims 1, 127-140, 150-153, 155-157, 205 and 213-218 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dunn (U.S. Patent No. 5,830,999) in view of Franke & Groeneveld (*Transit. Met. Chem.*, **1981**, *6*, 54-6) and Makovec *et al.* (*J. Med. Chem.*, **1992**, *35*, 3633-40). Dunn teaches that ligands that bind tightly and specifically to the two His^{B10} Zn^{2+} sites in insulin stabilize formulations of insulin hexamers for pharmaceutical use (abstract). Regarding claim 205, Dunn teaches compositions of fast acting insulin (column 7, line 7). Regarding claims 213-216, Dunn teaches compositions of at least 2 moles of zinc per mole of insulin (column 7, line 19) and at least 22 moles of phenolic compound per insulin hexamer (column 6, line 60). Regarding claims 217 and 218, Dunn teaches compositions with isotonicity agents and buffers (column, 7, line 11). Dunn does not teach the specific zinc ligands of the

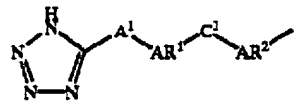
claimed invention. Franke & Groeneveld teach that tetrazoles can coordinate zinc. Makovec *et al.* teach the following tetrazole compounds:



4-Trz, R2=3,5-COOH; 4-Trz, R2=2,5-COOH; 4-Trz, R2=H, 4-Trz; R2=4-CN; and 4-Trz, R2=4-COOH, wherein Trz=1H-Tetrazol-5-yl. With respect to the formula in claim 127, K is a bond, M is an arylene, R^{40} is $C(O)NR^{41}R^{42}$, R^{41} is H, R^{42} is aryl substituted by R^{46}, R^{46} is COOH or CN, Q is a bond and T is hydrogen. It would have been obvious to one of ordinary skill in the art to combine the tetrazole ligands of Makovec *et al.* with the insulin hexamers of Dunn. The skilled artisan would have been motivated to do so given that Dunn teaches that ligands for the His^{B10} Zn^{2+} sites stabilize the hexamer form of insulin and Franke & Groeneveld teach that tetrazole containing compounds can coordinate zinc. There would have been a reasonable expectation of success given that the tetrazole compounds of Makovec *et al.* are functionally equivalent to the ligands of Dunn. Thus, the invention as a whole was clearly *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

12. Claims 1, 127-170, and 205-218 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dunn (U.S. Patent No. 5,830,999) in view of Olsen *et al.* (US 2003/0229120). Dunn teaches that ligands that bind tightly and specifically to the two His^{B10} Zn^{2+} sites in insulin stabilize formulations of insulin hexamers for pharmaceutical use (abstract). Dunn does not teach the specific ligands of the claimed invention. Olsen *et al.* teach novel ligands for the His^{B10} Zn^{2+} sites of the R-state insulin hexamer that are capable of prolonging the action of insulin

preparations. The ligands have the formula A-B-C-D-X wherein A is a functionality capable of reversibly coordinating to a His^{B10} Zn^{2+} site of an insulin hexamer and includes compounds of the formula

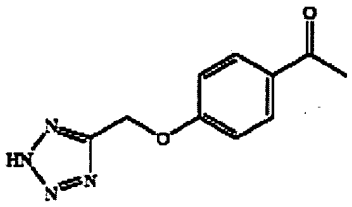


wherein A^1 is a valence bond, C_1-C_6-alkylene, -NH-C(=O)-A^2, -C_1-C_6-alkyl-S-, -C_1-C_6-alkyl-O-, -C(=O)-, or -C(=O)-NH-, wherein any C_1-C_6-alkyl moiety is optionally substituted by R^{1A}; A^2 is a valence bond, C_1-C_6-alkylene, C_1-C_6-alkenylene, or -C_1-C_6-alkyl-O-; R^{1A} is C_1-C_6-alkyl, aryl, wherein the alkyl or aryl moieties are optionally substituted by one or more halogen, cyano, nitro, amino; AR^1 is a valence bond, arylene or heteroarylene, wherein the aryl or heteroaryl moieties are optionally substituted by one or more R^{1B} independently; R^1B is selected from hydrogen, halogen, -CN, -CH_2CN, -CHF_2, -CF_3, -OCF_3, -$OCHF_2$, -OCH_2CF_3, -OCF_2CHF_2, -$S(O)_2CF_3$, -$OS(O)_2CF_3$, -SCF_3, -NO_2, -OR^1C, -NR^1CR^1D, -SR^1C, -$NR^1CS(O)_2$R.sup- .1D, -$S(O)_2NR^1CR^1$D, -S(O)NR^1CR^1D, -S(O)R^1C, -$S(O)_2R^1$C, -$OS(O)_2R^1$C, -C(O)NR^1CR^1D, -OC(O)NR^1CR^1D, -NR^1CC(O)R^1D, -CH_2C(O)NR^1CR^1D, -OC_1-C_6-alkyl-C(O)NR^1CR^1D, -CH_2OR^1C, -CH_2OC(O)R^1C, -$CH_2NR^1CR^1$D, -OC(O)R^1C, -OC_1-C_6-alkyl-C(O)OR^1C, -OC_1-C_6-alkyl-OR^1- C, -S-C_1-C_6-alkyl-C(O)OR^1C, -C_2-C_6-alkenyl-C(=O)OR^1C, -NR^1C-C(=O)-C_1-C_6-alkyl-C(=O)OR- ^{1}C, -NR^1C-C(=O)-C_1-C_6-alkenyl-C(=O)OR^1- C, -C_2-C_6-alkenyl-C(=O)R^1C, =O, -NH-C(=O)-O-C_1-C_6-alkyl, or -NH-C(=O)-C(=O)- -O-C_1-C_6-alkyl, C_1-C_6-alkyl, C_2-C_6-alkenyl or C_2-C_6-alkynyl, which may optionally be substituted with one or more substituents selected from halogen, -CN, -CF_3, -OCF_3, -OR^1C, and -NR^1CR^1D. aryl, aryloxy, aryloxycarbonyl , arylsulfanyl, aryl-C_1-C_6-alkoxy, aryl-C_1-C_6-alkyl, aryl-C_2-C_6-alkenyl, aroyl-

C_2-C_6-alkenyl, aryl-C_2-C_6-alkynyl, heteroaryl, heteroaryl-C_1-C_6-alky- l, heteroaryl-C_2-C_6-alkenyl or heteroaryl-C_2-C_6-alkynyl, of which the cyclic moieties optionally may be substituted with one or more substituents selected from halogen, -C(O)OR^1C, -CH_2C(O)OR^1C, -CH_2OR^1C, -CN, -CF_3, -OCF_3, -NO_2, -OR^1C, -NR^1CR^1D and C_1-C_6-alkyl; R^1C and R^1D independently are hydrogen, -OH, C_1-C_6-alkyl, C_1-C_6-alkenyl, aryl-C_1-C_6-alky- l or aryl, wherein the alkyl moieties may optionally be substituted with one or more substituents selected from halogen, -CN, -CF_3, -OCF_3, -O-C_1-C_6-alkyl, -C(O)-O-C_1-C_6-alkyl- , -COOH and -NH_2, and the aryl moieties may optionally be substituted by halogen, -C(O)OC_1-C_6-alkyl, -COOH, -CN, -CF_3, -OCF_3, -NO_2, -OH, -OC_1-C_6-alkyl, -NH_2, C(=O) or C_1-C_6-alkyl; R^1C and R^1D when attached to the same nitrogen atom may form a 3 to 8 membered heterocyclic ring with the said nitrogen atom, the heterocyclic ring optionally containing one or two further heteroatoms selected from nitrogen, oxygen and sulphur, and optionally containing one or two double bonds; C^1 is a valence bond, C_1-C_6-alkylene, -C_1-C_6-alkyl-O-, -C_1-C_6-alkyl-NH-, -NH-C_1-C_6-alkyl, -NH-C(=O)-, -C(=O)-NH-, -O-C_1-C_6-alkyl, -C(=O)-, or -C_1-C_6-alkyl-C(=O)-N(R^1E) wherein the alkyl moieties are optionally substituted by one or more R^1F ; R^1E and R^1F are independently selected from C_1-C_6-alkyl, aryl optionally substituted by one or more halogen, -COOH; $AR^2$is a valence bond C_1-C_6-alkylene, C_2-C_6-alkenylene, C_2-C_6-alkynylene wherein the alkyl, alkenyl and alkynyl moieties are optionally substituted by one or more R^{2A} independently; arylene, -aryloxy-, -aryloxy-carbonyl-, aryl-C_1-C_6-alkyl, -aroyl-, aryl-C_1-C_6-alkoxy-, aryl-C_2-C_6-alkenyl-, aryl-C_2-C_6-alkynyl-, heteroarylene, -heteroaryl-C_1-C_6- -alkyl-, -heteroaryl-C_2-C_6-alkenyl-, -heteroaryl-C_2-C_6- -alkynyl- wherein the aryl and heteroaryl moieties are optionally substituted by one or more R^{2A} independently; R^{2A} is C_1-C_6-alkyl, C_1-C_6-alkoxy, aryl, aryloxy, aryl-C_1-C_6-alkoxy, -C(=O)-NH-

C_1-C_6-alkyl-aryl, heteroaryl, heteroaryl-C_1-C_6-alkoxy, -C_1-C_6-alkyl-COOH, -O-C_1-C_6-alkyl-COOH, -S(O)$_2$R.sup.2B, -C_2-C_6-alkenyl-COOH, -OR^{2B}, -NO_2, halogen, -COOH, -CF_3, -CN, -$N(R^{2B}R^{2C})$, wherein the aryl or heteroaryl moieties are optionally substituted by one or more C_1-C_6-alkyl, C_1-C_6-alkoxy, -C_1-C_6-alkyl-COOH, -C_2-C_6-alkenyl-COOH, -OR^{2B}, -NO_2, halogen, -COOH, -CF_3, -CN, or -$N(R^{2B}R^{2C})$; and R^{2B} and R^{2C} are independently selected from hydrogen and C_1-C_6-alkyl. See paragraphs 548-568.

13. The species



is cited as a preferable form of A (paragraph 0070) as are several other specific compounds that fall within this general formula (examples 399-592).

14. Regarding claim 205, Dunn teaches compositions of fast acting insulin (column 7, line 7). Regarding claims 206-213, Olsen *et al.* teaches that the insulin is an analogue of human insulin selected from the group consisting of an analogue wherein position B28 is Asp, Lys, Leu, Val, or Ala and position B29 is Lys or Pro and des(B28-B30), des(B27) or des(B30) human insulin; the human insulin wherein position B28 is Asp or Lys, and position B29 is Lys or Pro; the insulin is des(B30) human insulin; the insulin is a derivative of human insulin having one or more lipophilic substituents; the insulin derivative is selected from the group consisting of B29-N^{ε}-myristoyl-des(B30) human insulin, B29-N^{ε}-palmitoyl-des(B30) human insulin, B29-N^{ε}-myristoyl human insulin, B29-N^{ε}-palmitoy- l human insulin, B28-N^{ε}-myristoyl Lys^{B28} Pro^{B29}

human insulin, B28-N^{ε}-palmitoyl Lys^{B28} Pro^{B29} human insulin, B30-N^{ε}-myristoyl-$Thr^{B29}Lys^{B30}$ human insulin, B30-N^{ε}-palmitoyl-$Thr^{B29}Lys^{B30}$ human insulin, B29-N^{ε}-(N-palmitoyl-.gamma.-glutamyl)-des(B30) human insulin, B29-N^{ε}-(N-lithocholyl-.gamma.-glutamyl)-des(B30) human insulin, B29-N^{ε}-(.omega.-carboxyheptadecanoyl)-des(B30) human insulin and B29-N^{ε}-(omega.-carboxyheptadecanoyl) human insulin; the insulin derivative is B29-N^{ε}-myristoyl-des(B30) human insulin. Regarding claims 213-216, Dunn teaches compositions of at least 2 moles of zinc per mole of insulin (column 7, line 19) and at least 22 moles of phenolic compound per insulin hexamer (column 6, line 60). Regarding claims 217 and 218, Dunn teaches compositions with isotonicity agents and buffers (column, 7, line 11).

15. It would have been obvious to one of ordinary skill in the art to combine the A ligands of Olsen *et al.* with the insulin hexamers of Olsen *et al.* and Dunn in the absence of the -B-C-D-X moiety. The skilled artisan would have been motivated to do so given that Dunn teaches that ligands for the His^{B10} Zn^{2+} sites stabilize the hexamer form of insulin and Olsen *et al.* teach that the A groups bind to the His^{B10} Zn^{2+} sites. There would have been a reasonable expectation of success given that the A compounds are functionally equivalent to the ligands of Dunn. Thus, the invention as a whole was clearly *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

16. The applied reference Olsen *et al.* has a common inventor and assignee with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was

derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131.

Double Patenting

17. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

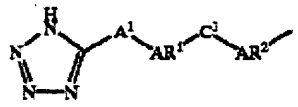
18. A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

19. Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

20. Claims 1, 127-170, and 205-218 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims of copending Application No. 11/226,870. Although the conflicting claims are not identical, they are not patentably distinct from each other because claims 1, 127-158, 166 and 170 are generic to all that is recited in claims 23-49, 53-57, 66 and 70 of copending Application No. 11/226,870. That is claims 23-49, 53-57, 66 and 70 of copending Application No. 11/226,870 fall entirely within the scope of claims 127-158, 166 and 170 or, in other words, claims 127-158, 166 and 170 are anticipated by claims 23-49, 53-57, 66 and 70 of copending Application No. 11/226,870. Specifically, claims 23-49, 53-57, 66 and 70 of copending Application No. 11/226,870 recite pharmaceutical

compositions comprising insulin and a ligand that binds reversibly to a His^{B10} Zn^{2+} site of an R state insulin hexamer wherein the ligand has the formula identical to that in claim 127 of the instant application. Claims 159-167, 167-169 and 205-218 overlap in scope with claims 1-43 of copending Application No. 11/226,870 but do not have a precise genus-species relationship with these claims. This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

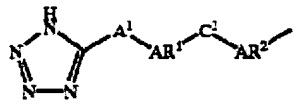
21. Claims 1, 127-170, 205 and 213-218 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 92-120, 137-139, 141-143, 147, 151, 152, 154, 155, 158, 159, 162, 165-173 and 175-186 of copending Application No. 10/332,541 in view of Dunn (U.S. Patent No. 5,830,999). The claims of the copending application are drawn to compounds of formula A-B-C-D-X wherein A is a functionality capable of reversibly coordinating to a His^{B10} Zn^{2+} site of an insulin hexamer and includes compounds of the structure



wherein the variables are defined above. Dunn teaches that ligands that bind tightly and specifically to the two His^{B10} Zn^{2+} sites in insulin stabilize formulations of insulin hexamers for pharmaceutical use (abstract). It would have been obvious to one of ordinary skill in the art to combine the A ligands of copending application 10/332,541 with the insulin hexamers in the absence of the -B-C-D-X moiety. The skilled artisan would have been motivated to do so given that Dunn teaches that ligands for the His^{B10} Zn^{2+} sites stabilize the hexamer form of insulin and the claims of copending Application No. 10/332,541 teach that the A groups bind to the His^{B10}

Zn^{2+} sites. There would have been a reasonable expectation of success given that the A compounds are functionally equivalent to the ligands of Dunn. This is a provisional obviousness-type double patenting rejection.

22. Claims 1, 127-170, 205 and 213-218 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-47 of copending Application No. 11/227,760 in view of Dunn (U.S. Patent No. 5,830,999). The claims of the copending application are drawn to compounds of formula CGr-Lnk-Frg1-Frg2-X wherein CGr is a chemical group which reversibly binds to a His^{B10} Zn^{2+} site of an insulin hexamer and includes compounds of the structure



wherein the variables are defined above (the '760 application uses the variables K, M, Q and T instead of A^1, AR^1, C^1, and AR^2 but the genus is equivalent and for simplicity will not be repeated here). Dunn teaches that ligands that bind tightly and specifically to the two His^{B10} Zn^{2+} sites in insulin stabilize formulations of insulin hexamers for pharmaceutical use (abstract). It would have been obvious to one of ordinary skill in the art to combine the CGr ligands of copending application 11/227,760 with the insulin hexamers in the absence of the Lnk-Frg1-Frg2-X moiety. The skilled artisan would have been motivated to do so given that Dunn teaches that ligands for the His^{B10} Zn^{2+} sites stabilize the hexamer form of insulin and the claims of copending Application No. 11/227,760 teach that the CGr groups bind to the His^{B10} Zn^{2+} sites. There would have been a reasonable expectation of success given that the CGr compounds are

functionally equivalent to the ligands of Dunn. This is a provisional obviousness-type double patenting rejection.

Conclusion

23. No claims are allowed.
24. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christina Marchetti Bradley whose telephone number is (571) 272-9044. The examiner can normally be reached on Monday through Friday, 8:30 A.M. to 5:00 P.M.
25. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang can be reached on (571) 272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.
26. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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